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Recent Approaches in Cancer Therapy: An Overview

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ABSTRACT

Cancer is currently one of the major diseases that has gained a lot of scientific attention. Conventional cancer therapeutics involve surgical removal of tumors from patients followed by chemotherapeutic treatment. In the use of anticancer drugs during the chemotherapy process, patients often suffer from a variety of undesirable side effects including damage to normal organs. Thus, there is an urgent need for the development of novel strategies to overcome these side effect issues. Malignant diseases are one of the major causes of death in the western world. Patients are treated by surgery, radiation and chemotherapy. Chemotherapeutic treatment is used to decrease the tumour burden and to eliminate malignant cells. However, in most cases, resistance against chemotherapy develops. Therefore, there is a permanent need for new additional treatment strategies and chemotherapeutic combination regimens. In the present review article, the authors try to highlight the most promising approaches and summarize a selection of potential targets and compounds which might become alternative treatment options against malignant diseases.

Keywords: Cancer, Chemotherapy, Radiation, Malignant diseases, Novel Strategies.

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INTRODUCTION

Cancer has become a curse for the whole world and about 7.6 million people are dying due to this disease every year. It is estimated that the death may increase up to 9.0 millions and 11.0 millions in 2015 and in 2030, respectively [1]. About 70% deaths are due to only cancer in the developing countries owing to poor availability of prevention, diagnosis and treatment. Currently, many medications are being used as individual or in combination. Most commonly used medicines are cisplatin, carboplatin, bleomycin, 5- fluorouracil, doxorubicin, dactinomycin, 6-mercaptopurine, paclitaxel, topotecan, vinblastin, etoposide etc.[2,] which are of synthetic or natural origins. Of course, these treatments are effective but suffer from certain draw-backs such as fast drug release, short blood circulation time and non-target specificity. Besides, these have some serious side effects and, sometimes, disturb normal cells. The past decade has seen enormous advances in our understanding of the basic biology of cancer. These include knowledge of cancer genetics, in particular of oncogenes and tumour suppressor genes, the processes of cancer cell metastasis and angiogenesis, and tumour immunology. These advances present great opportunities and challenges in many areas of oncology.

Table 1: New cytotoxic agents introduced into practice and/or still in development in the 2000s[39]

Class Drug (Trade name)	**Initial indications**
Anlimelabolites	
Fludarabine (Fludara™)	lymphomas, chronic lymphocytic leukemia
Cladribine (Leustatin™)	hairy cell leukemia, lymphomas
Pentostatin (Nipent™)	hairy cell leukemia
Gemcitabine (Gemzar™)	pancreatic cancer
Capecitabine (Xeloda™)	breast cancer
Raltitrexed (Tomudex™	colorectal cancer
Platinums	
Carboplatin (Paraplatin™)	ovarian and lung cancers
Oxaliplatin (Eloxatin™)	colorectal cancer
Taxanes	
Paclitaxel (Taxol™)	ovarian, breast, lung cancers
Docetaxel (Taxotere™)	breast and lung cancers
Topoisomerase I inhibitors	
Topotecan (Hycamtin ™)	ovarian and lung cancers
Irinotecan (Camptosar™)	colorectal cancer
Vinca alkaloids	
Vinorelbine (Navelbine™)	breast and lung cancers

New cytotoxic agents

As shown in Table 1, the 200s0s was a very productive decade for the development of new cytotoxic anticancer drugs [3,4]. Three new purines (fludarabine, cladribine, and pentostatin) were introduced for hematological malignancies [5,6]. The new pyrimidine analogue gemcitabine has shown a broad spectrum of clinical antitumour activity, in addition to its initial approved indication in pancreatic carcinoma[7]. Capecitabine as an oral prodrug of 5-fluorouracil (5-FU) has shown significant activity in breast cancer [8, 9.]Raltitrexed is the first of a series of new agents targeted primarily at thymidylatesynthase[10]. Oral therapy with modulators of 5-FU metabolism or activity will continue to be a focus of development, including the potent inhibitor of dihydropyrimidine dehydrogenase eniluracil with 5-FU and the combination of tegafur/uracil/5-FU/leucovorin[11]. The taxanes, paclitaxel and docetaxel, are continuing to be studied in a wide range of tumours [12,13]. The topoisomerase I inhibitors represent a new class of agents notable for the activity of irinotecan in colorectal cancers, and topotecan in refractory ovarian cancers [14,15]. Many of these new drugs, as well as the Vinca alkaloid vinorelbine, are active in lung cancers, and their roles in combination with platinum drugs in particular will be a focus of intense clinical research for the next several years [16,17.]

Monoclonal Antibodies

The promise of monoclonal antibodies as cancer therapies is finally being fulfilled, after almost two decades of clinical trials [18]. The anti-CD20 antibody rituximab (Rituxan™) has produced a 48% remission rate in a pivotal phase II trial in low-grade B-cell lymphomas, with remissions lasting approximately a year [19,20]. Trials of rituximab in combination with chemotherapy are in progress. At the same time, the anti-HER2/neu antibody trastuzumab (Herceptin™) has demonstrated efficacy both as a single agent and in combination with chemotherapy in women with advanced breast cancer [21,22]. The apparent synergistic antitumour effect of trastuzumab with paclitaxel, its exacerbation of the cardiotoxicity of doxorubicin, and its role in adjuvant therapies are the subjects of current research. Several other monoclonal antibodies and radioisotopic conjugates with monoclonal antibodies are currently in various stages of investigation [23].

Oncogene targeted agents, gene therapies, and gene expression microarrays

Knowledge about the molecular basis for oncogenesis is being translated into novel therapies which are in early stages of clinical development. Several companies are developing small molecule inhibitors of farnesyl transferees inhibitors, an enzyme which is essential for the proper anchoring and function of the ras oncogene in the cell membrane [24]. The identification of

mutations in the p53 gene in the majority of human cancers has led to a variety of approaches, including re-introduction of a normal p53 using gene therapy vectors[25,] as well as the use of a defective adenovirus which selectively replicates in and kills cells with mutant p53[26]. Other gene therapy methods depend upon the transfection into tumour cells of microbial genes for enzymes which activate prodrugs, such as the herpes simplex thymidine kinase gene with gancyclovir[27], or the cytosine deaminase gene with fluorocytosine[28]. An inherent liability with these gene therapy approaches is the localized nature of the treatment, involving injections of cells or vectors directly into large, visible tumours. Unfortunately, this does not address the problem of system micrometastases, which limits the survival of most patients who die of cancers.

Targeting Specific Molecular Alterations. Lessons Learnt from their Clinical Application

For almost a century, systemic therapy of cancer has been dominated by the use of cytotoxic chemotherapeutics. Most of theses drugs are DNA-damaging agents that are designed to kill or inhibit rapidly dividing cells. They are often administered in single doses or short courses of therapy at the highest doses possible without no life-threatening levels of toxicity, called "Maximum Tolerated Dose" (MTD) [29,30]. The high doses of these MTD chemotherapy schedules require an extended treatment-free period to permit recovery of normal host cells. Despite the last advances, we know that the genetic instability and high mutation rate of cancer cells ensure that chemotherapy, directed mainly or solely at the cancer cell, still carries a high risk of selection for drug-resistant cell clones [31]. While the attempts to improve the pace of discovery of cytotoxic agents proceeded in the late 1980s, at present molecular and genetic approaches to understanding cell biology are addressed to uncover entirely new signalling networks that regulate proliferation and survival. The increasing knowledge has lead to a more elaborate concept of tumor cell characteristics including self dependence on positive regulatory signals; lack of response to growth inhibitory signals, limitless proliferation, resistance to apoptosis, capability of getting nutrients and oxygen by angiogenesis, and the ability to invade and establish distant metastasis[32]. The elucidation of the molecular basis of cellular transformation, the concept that cancer is basically a genetic disease of somatic cells and that these genetic and epigenetic alteration sunderly an aberrant transcription program has created a novel framework that is changing clinical practice. Also the recognition that cancer cells need their microenvironment (i.e. fibroblasts, vessels, macrophages, lymphocytes, etc) to fully display their phenotype has opened the door to new therapeutic strategies.

Targeted Therapy antiHER2

This is probable the first demonstration of a successful targeted therapy. HER-2/neu belongs to a family of four trans membrane receptor tyrosine kinases that mediate cell growth, differentiation, and survival [33.] Overexpression of the HER-2/neu protein, amplification of the her-2/neu gene, or both occurs in 20%–25% of breast cancers [34] HER- 2/neu-positive breast cancer is an aggressive type that has a high rate of recurrence and short disease free intervals after adjuvant (postoperative) chemotherapy. The ErbB2 receptor is also an accessible extracellular target for specific anticancer treatment. A range of targeting strategies has been investigated, the majority being directed at the ErbB2 extracellular domain, with the therapeutic mAbtrastuzumab having received regulatory approval.

Table: 2 List of various drugs used in targeted therapy [40-41]

Therapeutic Group	DRUG	Target Group	Target
Monoclonal Antibodies	Trastuzumab	B	Her-2
	Cetuximab	B	EGFR
	Bevacizumab (Angiogenesis inhibitor)	B	VEGF
Chemotherapy/radiotherapy	Multiple	A, D, E	DNA, mitotic complex
Endocrine therapy	Tamoxifen	B	ER
	Fulvestrant	B	ER
	Aromatase Inhibitors	B	Aromatase
Small Molecules	Sunitinib	A, C	c-kit, PDGFR, VEGFR
	Imatinib	C	c-kit, PFGFR
	Lapatinib	C	Her-2
	Erlotinib	C	EGFR

Virotherapy

In parallel with the development of the new targeted therapies, the use of biologicals, while lagging behind, has made significant advances in their path to clinical evaluation. A first use of viral vectors has been to improve chemotherapy effectiveness, by achieving a sufficiently high concentration of the anticancer drug close to the malignant cells. Suicide gene therapy is one of the novel alternatives to increase drug selectivity towards cancer cells. Approaches using deactivated drugs are known as gene-directed enzyme prodrug therapy (GDEPT). In the first step, a gene encoding a foreign enzyme is delivered to the tumor for expression. In the second step, a prodrug is administered that can be activated to release a cytotoxic drug by the enzyme that has been expressed in the tumor. Two GDEPT systems that have been investigated

extensively are the herpes simplex virus thymidine kinase–ganciclovir (HSV-TK–GCV) combination, and the cytosine deaminase– 5-fluorocytosine (CD–5-FC) combination; both have been tested in clinical trials [35]. One of the foremost advances of the last half of this decade has been the ability to profile the expression of thousands of genes by microarrays [36,37]. These new gene chip technologies are likely to revolutionize our understanding of cancer mechanisms, cellular responses to therapies, and predictions of genetic predispositions and outcomes.

CONCLUSION

Of course, chemotherapy for cancer is in its developmental stage and various medicines are in market but, unfortunately, have different side effects and toxicities to normal cells. Approximately, two thirds of cancer patients will defeat their disease. The combined use of surgery, radiation therapy and chemotherapy accounts for most of cured cases. In the last fifty years, endocrine blockade herein reviewed for breast cancer and cytotoxic therapy have played an increasing role. The advent of targeted therapies based on a comprehensive knowledge of neoplastic transformation has already provided with two successful examples such as trastuzumab for ErbB2 positive breast cancers and imatinib for Chronic Myelogenous Leukemia. In the same line, the recent approval for antiEGFR therapies is also positive although their overall benefit is still small. A high number of novel drugs are in the pipeline awaiting clinical development, meanwhile, novel strategies such as the antiangiogenic approach and virotherapy are reaching the clinical setting.

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